Surface and Coatings Technology 112 (1999) 278–285

Biomaterials modification by ion-beam processing

F.Z. Cui *, Z.S. Luo

Department of Material Science and Engineering, Tsinghua University, Beijing 100084, People's Republic of China

Abstract

Biomaterials modification by ion-beam processing is becoming popular for improving medical device function, biocompatibility and as a new mutation breeding method. Ion-beam-based processes, such as ion implantation and ion-beam assisted deposition (IBAD) can provide beneficial surface layers with desirable properties without detrimentally affecting the bulk properties. Ion implantation has been successful in biomaterials modification, such as in improving the wear resistance of artificial joint components, in improving wettability, anticoagulability, anticalcific behavior of biomedical polymers, and in minimizing biofouling of medical devices, etc. IBAD has been used to prepare hydroxyapatite coatings with high adhesive strength on substrates of several implant materials. Biocompatible diamond-like carbon coatings and C–N films, antibacterial coatings and sealant coatings have also been produced by this technique. This paper reviews the present status of applications of the ion-beam process in modifying the surface of biomaterials, as well as the effects induced by ion-beam irradiation to crop seeds, cells and microbes.
© 1999 Elsevier Science S.A. All rights reserved.

Keywords: Biomaterials; Ion-beam process; Mutation breeding; Surface modification

1. Introduction

Biomaterials modification by the ion-beam process including plasma surface treatment has recently become an interesting topic in the field of surface engineering [1,2]. There are three main reasons that induct this trend. First, the importance of surface-engineered biomaterials to the longevity of medical implants has been recognized by both major medical device companies and more and more patients. In recent years, some specialized companies offered surface treatments to the medical market in several countries. We take an example to illustrate the importance. In bone replacement, especially long bone and joint replacement, metal implants are widely used to take the unsubstituted position. Although the metallic orthopedic implants may have excellent bulk properties such as ideal strength and elasticity, it has relatively poor surface properties, e.g. poor wear resistance and limited biocompatibility. It is therefore necessary to make a compromise between the bulk and surface properties. In the case of hip replacement, the wear debris from the implant is one of the essential factors for the aseptic loosening which is a frequent cause of failure of the prosthetic implants. It is generally accepted that improving the wear resistance and biocompatibility of the implants by surface engineering is an optimal option.

Second, the range of biomaterials has been significantly extended from synthesized materials of metals, ceramics and polymers to those including biological materials. For example, the newest definition of biomaterials is "either naturally occurring materials in living organisms or materials designed to repair humans" [3]. Recently, a number of new effects of ion implantation on biomaterials have been observed and used in improving crops and modifying microbes [4]. However, the interaction mechanisms between low energy (keV) ions and biological systems is still unclear due to the complex hierarchical structure of biological systems.

Third, ion-beam processes including plasma treatment which is based on ionized particle bombardment have been particularly successful in biomaterials modification, compared to other available surface treatment processes such as conventional coating process, nitriding, laser process, etc. This may be a result of the advantage of ion-beam process, e.g. exact process control, low temperature processing, versatility of ion species, non-equilibrium process and reliability. In general, the cost of the ion-beam process is relatively high, as it involves a

* Corresponding author. Tel: +86 10 62784546;
Fax: +86 10 62771160; e-mail: cuifz@sun.ihep.ac.cn

0257-8972/99/$ – see front matter © 1999 Elsevier Science S.A. All rights reserved.
PII S0257-8972(98)00763-4

vacuum chamber. However, the concerns on the life quality in many cases make the cost of the ion-beam process less problematic.

In this article, techniques and applications of surface modification of biomaterials based on the ion-beam process are discussed. In particular, the technologies of ion implantation and ion-beam assisted deposition (IBAD) are described. Their applications in the biomedical field are introduced. Also, some applications of ion implantation in the field of gene mutation of seed are reported.

2. Ion implantation process

2.1. Overview

In the ion implantation process, ions are accelerated to a certain energy and directed toward the surface of the target materials. The energy of the ions before they penetrate the surface is typically between 20 and 200 keV. Ions with such a level of energy would penetrate the substrate of solid materials like metals, ceramics and polymers to a depth in the magnitude of several hundred nanometers. However, the situation is quite different in the case of ion penetration in biological systems, where ions can penetrate a depth of several ten microns [4]. The effects induced by the ion implantation in biological system will be discussed in Section 2.4.

Up to date, ion implantation has been successfully applied in metal and polymer biomaterials. In metal biomaterials, physical procedures such as atomic and nuclear collisions often lead to the formation of highly disordered and sometimes amorphous structure in the near-surface region. Chemical procedures such as new chemical bonds formed between the substrate atoms and the implanted ions lead to the formation of new surface phases with mechanical and chemical properties that are significantly different from the bulk materials. In the polymer biomaterials, similar procedures happen, but the situation is more complicated. For the polymer substrate, there are two major competing processes: chain cross-linking and chain scission. The cross-linking process creates a three-dimensionally cross-linked surface layer with much higher hardness and much improved wear resistance. While the scission process generally leads to the scission of the long molecular chain, which would eventually result in polymer degradation. There are other applications of implantation which are recognized and put into practice by more and more researcher. That is to produce a specific functional chemical group at the surface of the polymer to improve the surface wettability and biocompatibility of biomaterials.

The entire process of ion implantation is conducted in a high vacuum environment. Ion species, the ion-beam energy, the dose (or influence), and the beam current density (or flux) are the four major ion implantation parameters. By accommodation of these parameters, a great variety of effects can be obtained on the substrate.

Ion implantation has numerous advantages for modification of a biomaterial surface. The primary advantage is selective surface modification without detrimentally affecting bulk properties. The process is also extremely controllable, reproducible and clean enough for medical devices. Because of the low substrate temperature during the ion implantation process, the product dimensions are not affected. The drawbacks of this process are the high cost and the relatively shallow depth of modification. Additionally, ion implantation is a line-of-sight technique, so the uniform modification of those products with complicated geometries requires extraordinary sophisticated toolings.

2.2. Applications in metal biomaterials

A traditional application of ion implantation is the surface modification of metal materials. Each year about one million total joint arthroplasty procedures are performed in the world [2] to recover joint function of individuals primarily with severe arthritis or joint injury. Most artificial joints consist of a metallic component articulating against a polymer. The metallic component is mainly made from either titanium/titanium alloy or cobalt–chromium (Co–Cr) alloys; the polymer component is mainly ultrahigh molecular weight polyethylene (UHMWPE). The main problem existing in the artificial joints is the prosthetic wear debris which is believed to be the major reason for aseptic loosening [5–7]. This problem has long been recognized, but only in the last several years has it received significant attention from manufacturers, surgeons and researchers. For the promotion of the wear resistance of the metallic components in artificial joints, ion implantation has been widely used.

Titanium and its alloys are among the most biocompatible metallic materials; they also have good corrosion resistance, excellent fatigue strength, excellent formability and machinability, low density and high modulus of elasticity. However, as mentioned above, the wear resistance of titanium and its alloy is relatively low. Ion implantation of metal materials (such as titanium) can harden the surface and reduce the friction coefficient, ultimately improving the wear resistance [8–11]. Hardening is attributed mainly to the formation of hard-phases of nitride, carbide and oxide precipitates. Low friction coefficients come from physical changes (as the adjustment of the crystalline structure) that occur in the near-surface region of the materials. Fig. 1 depicts the early wear test results from a pin-on-disk experiment of a titanium specimen in distilled water [8]. Distilled water is used to simulate the environment around the joints

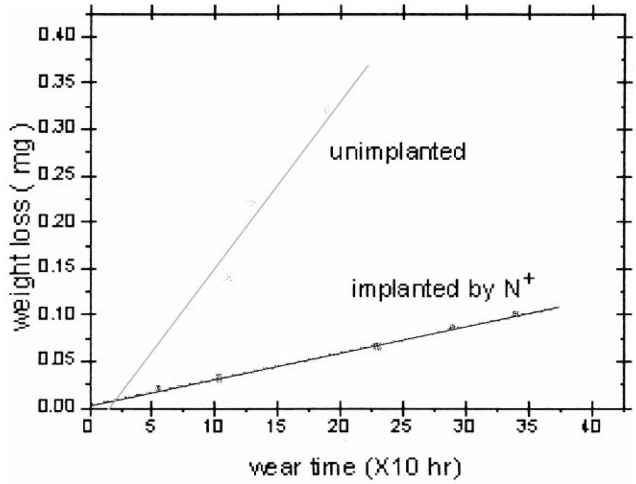

Fig. 1. Weight losses as a function of wear time for Ti–6Al–4V alloy in distilled water. In this pin-on-disk experiment, wear time of one hour corresponds to a sliding distance of 450 m.

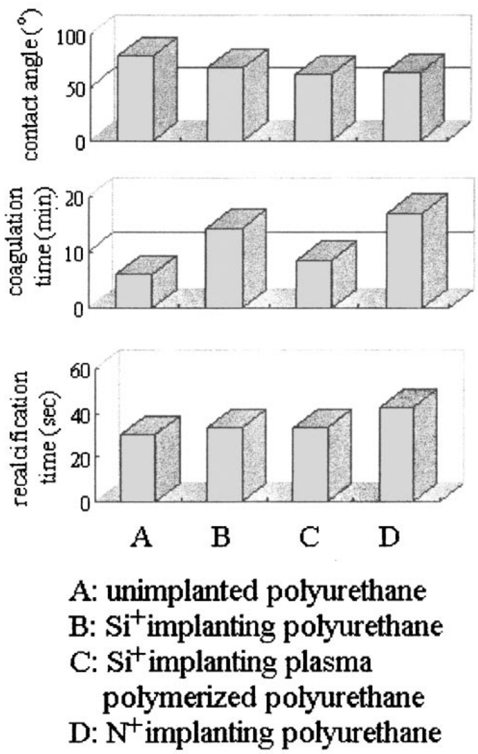

Fig. 2. Wettability, anticoagulability and anticalcific behavior of polyurethane with and without Si ions implantation. Decrease of contact angle, and increase of the coagulation time and recalcification time are observed in all groups comparing to the control.

for it has a viscosity close to that of the synovial fluids. It shows that by the N^+ implantation modification in the surface of titanium, the wear rate is reduced to 20% of its unimplanted value. It is reported [12] that the wear resistance of titanium can be further improved by an order of magnitude. Simulation studies [13] of the hip and knee joint confirm the above mentioned research. Practical application of this treatment has been executed for several years.

For other metal biomaterials, e.g. 316L stainless steel, similar improvements were obtained. It has been demonstrated [14] that an order-of-magnitude improvement in the wear resistance can be achieved for 316L stainless steel.

Co–Cr orthopedic prostheses are durable and wear resistant. However, the mating component of UHMWPE easily wears down over time owing to articulation against the Co–Cr component. A successful surface modification solution [15] in this case is to conduct ion implantation treatment in the surface of the Co–Cr component. Studies [2] showed that the ion implantation process alerts the dynamics of fluid film lubrication in the metal–polymer couple and results in the decrease of the coefficient of friction and in turn, reduces the wear. Ion implanted Co–Cr orthopedic products have gained commercial use since 1990.

2.3. Applications in polymer biomaterials

Polymers are another type of material that have gained extensive application in biomedical materials such as artificial blood vessels and artificial heart valves, due to their conformity to the organism. However, polymers at present have many deficiencies, e.g. low mechanical strength and poor wear resistance. Ion implantation presents a hopeful solution to eliminate these deficiencies. Satisfactory results have been achieved by ion implantation [2,16–21] over recent years in several polymer biomaterials like silicone rubber and polyurethane. It succeeds in improving wettability, anticoagulability, anticalcific behavior of polyurethane, and critical surface tension of silicon rubber which is thought to be a primary cause for the biofouling.

Polyurethane has been used in the medical field for many years. It exhibits several attractive properties, e.g. well tolerated under implant situation, durable enough to withstand continuous stress and flexing, and availability. On the other hand, its blood compatibility and anticalcific behavior are far inferior to those of body organs. Ion implantation has been successfully used [19–21] to improve the wettability, anticalcific behavior and blood compatibility. Fig. 2 shows the improvement of the wettability, anticoagulability and anticalcific behavior of polyurethane by ion implantation. Si^+ and N^+ were used in the experiments. In this study, one group (group c) of samples was treated by hexamethyldisiloxane plasma polymerization before ion implantation. All three groups show a decrease of contact angle, and increase of the coagulation time and recalcification time comparing to the control group.

Silicon rubber is the material of choice for a long-term indwelling catheter for its long history of biocompatibilty and its superior flexibility. However, it is tacky in the surface and prone to biofouling which is believed to be an important cause of the clinic failure of catheter replacement surgery. Many studies [2] have demonstrated the efficiency of ion implantation in reducing biofouling of silicon rubber.

2.4. Applications in biological systems

Some new effects of ion implantation into biological samples of crop seeds, cells and microbes have been observed in recent years [4]. When crop seeds were irradiated by energetic ions, e.g. 30 keV, radiation at a proper dose could promote their germination, and an overload dose would result in damage. This is a universal phenomena as well as γ-ray irradiation effects. However, it was recognized that a higher mutation rate and wider mutational spectrum can be obtained with greater survival rate of the seeds by ion implantation than by ionizing irradiation (X-rays, γ-rays). Table 1 gives an example in the case of four rice seeds. It is seen from Table 1 that both the survival rate in the current generation (M1) and the frequencies of the chlorophyll mutation in the second generation (M2) are remarkably higher by using ion implantation than with γ-rays. Furthermore, the chlorophyll mutation spectra indicated by the proportion of albina, xintha and striata are obviously different. The research on the mutation induced by low energy ions had been carried out at various levels, e.g. in population genetics, single character and single gene levels. In a recent investigation on sequence analysis of lacZ$^-$ mutations induced by ion-beam irradiation in double-stranded Mi3mp18DNA, the molecular mechanism of mutation induced by the ion beam has been detected [22]. Although the detailed process of ion-radiation mutation at microstructural, cell and molecular biological levels is still not understood well. The mutation effect of ion-beam radiation has been widely proved in many crops and microbes and has developed into a mutation breeding method.

3. Ion-beam assisted deposition

3.1. Overview

Ion-beam assisted deposition (IBAD) is a vacuum deposition process that combines physical vapor deposition (PVD) with ion-beam bombardment. Fig. 3 is a schematic drawing of a polyfunctional IBAD system [23]. The major feature of IBAD is bombardment with a certain energy (ranging from several hundred to several thousand eV) ion beam during the deposition of coating. There are many parameters that affect the composition, structure and mechanical and chemical properties of the as-deposited coating in the IBAD process, among which ion bombardment is the key factor. The major processing parameters are coating materials, evaporation rate or sputtering rate, ion species, ion energy and ion beam current density.

The most attractive characteristic of IBAD is that it is able to prepare bio-coatings with much higher adhesive strength to substrate comparing to a traditional coating method, e.g. plasma spraying under low temperature conditions, ion beam sputtering deposition (IBSD) and PVD. This is due to the interaction between the coating atoms and the substrate atoms which results in an atom-intermixed zone (as shown in Fig. 3) in the coating/substrate interface. Like ion implantation, it also possesses the advantages of low substrate temperature and high reliability and reproducibility, without adversely alerting the bulk attributes. Another attractive feature of the IBAD process is its superior control over coating microstructure and chemical composition. The primary limitation to its popularization for commercial application at present is its high cost.

3.2. Applications in hydroxyapatite coating preparation

Hydroxyapatite coatings on titanium alloy have been widely used for years. Its most attractive feature is that it possesses good biocompatibility of hydroxyapatite and good mechanical strength of titanium alloys. To prepare the hydroxyapatite coatings on titanium (or its

Table 1
Effects of ion implantation[a] and γ-rays[b] on the survival rate in M1 and chlorophyll mutation rate in M2 for rice

Varieties	Survival rate (%)			Mutation rate (%)		Albina		Xantha		Striata	
	CK	I.B.	γ-rays	I.B.	γ-rays	I.B.	γ-rays	I.B.	γ-rays	I.B.	γ-rays
02428	88.9	79.0	69.3	0.73	0.32	24.82	63.64	64.96	5.45	10.22	30.2
Fu8-1	90.0	84.8	75.1	0.38	0.34	26.02	58.02	11.38	13.85	62.6	28.4
8619	92.0	85.0	76.5	1.22	0.78	23.60	59.20	9.55	9.20	66.8	31.6
Average	90.3	82.9	73.6	0.78	0.48	24.9	60.5	28.6	9.5	46.5	30.0

[a] I.B.: ion implantation mutation, 7×10^{16} ions cm^{-2}, N$^+$ with 35 keV.
[b] γ-rays, dose is 300 Gy.

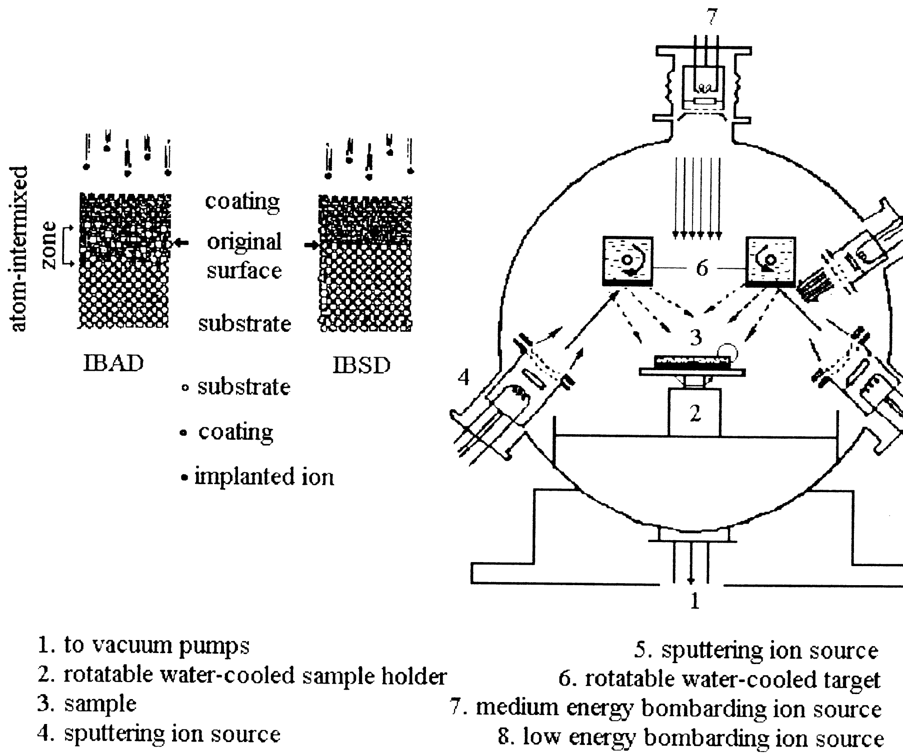

Fig. 3. Schematic drawing of the polyfunctional IBAD system and the process of IBAD.

alloys), many coating-produced methods have been undertaken, among which plasma spraying is most frequently used. However, long-term clinical follow-up has demonstrated that there are significant deficiencies in the plasma sprayed hydroxyapatite, which leads to limited longevity of the replacement devices, with shorter life spans occurring in young, active individuals. The primary deficiency of the plasma sprayed hydroxyapatite coating is its limited adhesive strength to the substrate. IBAD is reported [24] to be able to promote the coating/substrate adhesive strength to a much higher level than the plasma spraying method and other conventional methods.

Fig. 4 [24] displays the results of the scratch test of hydroxyapatite-coated Ti–6Al–4V specimens which were prepared by IBAD and ion beam sputtered deposition (IBSD), respectively. The critical load of IBAD coating is nearly twice that of control specimens. It reveals that IBAD coating possesses higher adhesive strength to substrate than coatings prepared by other processes.

Similar results have been obtained of hydroxyapatite coating on alumina [25] and UHMEPE [26] by the IBAD technique. An antimicrobial ceramic coating [27] has been recently investigated by our group using the IBAD process. It is a hydroxyapatite-based coating, in which the calcium ions are partly exchanged by the silver ions. In antibacterial tests of the coating, distinct inhibition regions of *E. coli* and *S. Aureus* were observed indicating good bacteria-inhibitation of the coating. This result is similar to the report [28] on the antimicrobial effects obtained by IBAD silver-based surface treatment.

3.3. Application in DLC film and C–N film

Diamond-like carbon (DLC) films possess novel properties, e.g. chemically inert, electrically resistant and optically transparent, among which extreme high hardness and low friction coefficient are their attractive characteristics for biomedical researchers. Many researchers have investigated the biocompatibility of DLC. They found that DLC films have good biocompatibility for various types of cells. A preliminary study [29] of the behavior of DLC in the context of joint replacements also shows that DLC film can operate as low-friction bearing surfaces. IBAD DLC films with strong adhesive strength to the substrate had been synthesized and were proved to be biocompatible [30,31].

Similar to DLC films, C–N film is also extremely hard and wear resistant. Although biomedical research on C–N film is in its infancy, its extremely high hardness and low friction make it an attractive candidate for use in the surface of a artificial joint component. A preliminary study [31] shows that it has good biocompatibility with osteoblast. Cell attachment, spread and proliferation on amorphous C–N film without apparent impairment of the cell physiology and detectable change of

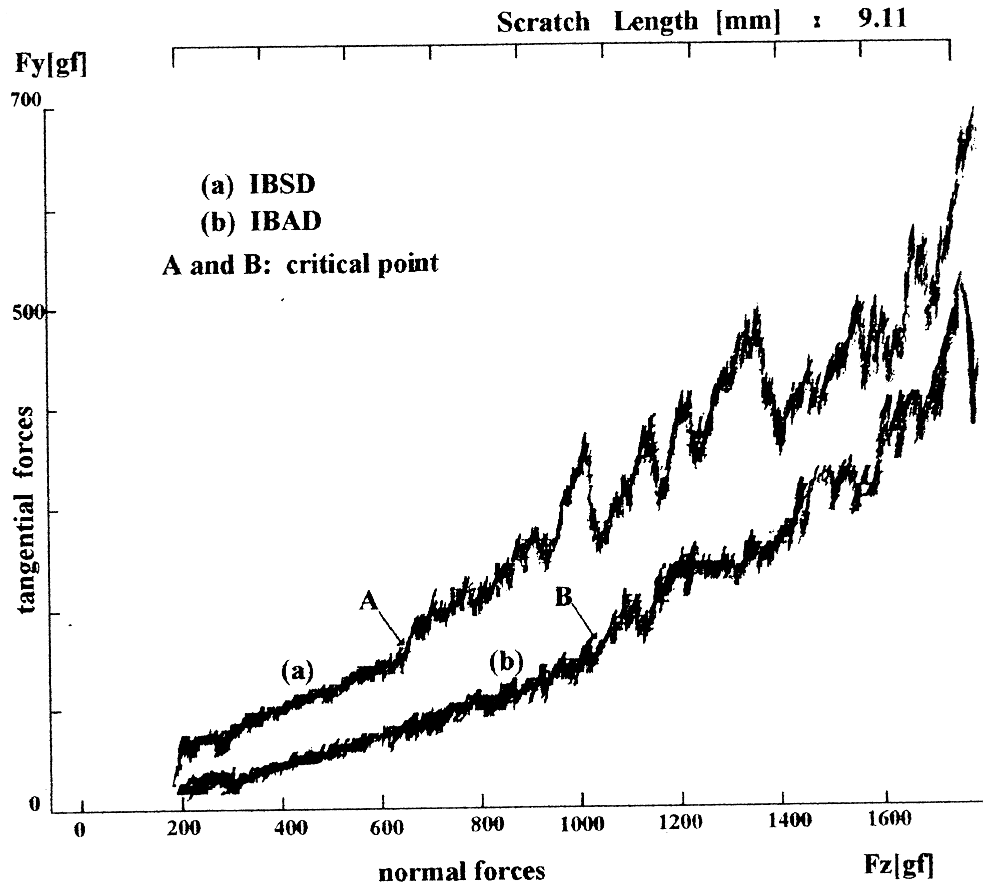

Fig. 4. Fz–Fy curve of scratch test from specimen prepared by (a) IBSD and (b) IBAD. Arrows A and B indicate the points where coating removal first occurs. The critical load for IBSD is 660 gf and for IBAD is 1050 gf. The loading speed was 2 kg min^{-1}.

morphology comparing to that of cells in the control is observed in this preliminary study.

3.4. Applications for other coatings

Infection is an important problem existing in surgery, especially in the replacement of artificial organs. IBAD methods provide a silver coating on catheters and other implantable medical devices which is infection-resistant [2]. The advantage of IBAD silver coating in this application is that it prevents bacteria attachment to the biomaterial surface and yet has a minimal leaching rate, providing a safe and long-lasting effect. Clinical trials for the coating have been performed recently. It demonstrated the effectiveness of IBAD silver coatings for preventing infection.

Another application of the IBAD method is to prepare sealant coatings [2] (as alumina coating) on the surface of polymer biomaterials to prevent oxygen and water vapor permeation. The features of bioinert, thin, clear and dense IBAD ceramic coating qualify it for this purpose. The potential use of the coating is in drug vials, and polymer bags used for collecting blood and other biological fluids.

4. Other ion-beam-based processes for biomaterials

Another ion-beam-based process is ion beam texturing (IBT). IBT is based on ion sputtering, which is the process of removing atoms from a solid surface by ion bombardment at a certain energy. The typical ion dose used in texturing is an order of magnitude higher than that used in ion implantation. The ion energy used is about several hundred to several thousand eV.

It is recognized that the surface topology of the cell scaffold materials has significant effects on cell behavior and on cell function [32]. IBT has the ability to create desirable microfeatures and macrofeatures on the biomaterials to meet the requirement of biocompatibility in vivo. By the use of a electroformed screen mesh mask, various patterns can be copied from the mesh to the surface: the atoms in the area without the mask being removed and the area with the mask surviving. Fig. 5 shows two examples. Although the relation between morphology of biomaterials and their biomedical behavior in vivo is still unclear, it is believed that the morphology plays an important role in the biocompatibility of biomaterials in vivo. IBT will be paid more attention in the field of tissue engineering materials.

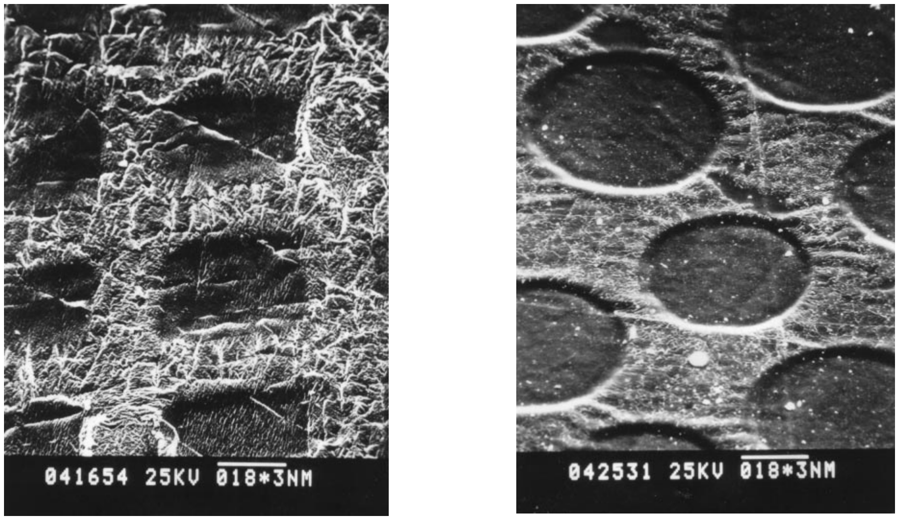

Fig. 5. The SEM morphology of the silicon rubber modified by the ion-beam texturing process with electroformed screen mesh mask of square (a) and round (b) meshes. The energy of the Ar ion beam used was 1 keV.

5. Conclusion

We have described the present status of the applications of ion-beam processes in the field of biomaterials and bio-engineering. Ion-beam processes possess the ability to optimize the surface properties without impairing the bulk attributes. They have many advantages over conventional methods, such as low temperature, cleanliness, high reliability and reproducibility. Furthermore, the most striking characteristics of this technique are a high degree of control over the quality of the modified layer and the high adhesive strength between the modified layer and the bulk materials.

Ion implantation has been successfully used for the surface treatment of metallic orthopedic prosthesis and has been put into clinical practice for several years. In addition to its achievement in metallic biomaterials, it has also shown the ability to improve wettability, anticoagulability and anticalcific behavior, and to minimize biofouling of medical polymers. Another field in which ion implantation manifests its virtues is genetic engineering. In China, great accomplishment has been made in mutation breeding of some crops and microbes by low energy ion irradiation.

IBAD embodies its value in the preparation of biocompatible coatings that bond strongly to various substrates. Its application in biomaterials is still increasing. Hydroxyapatite coatings have been prepared by this method. Such coatings exhibit much higher adhesive strength to substrate comparing to those prepared by other techniques. IBAD is also used to produce biocompatible DLC films and C–N films which have potential biomaterial use in medical devices. Moreover, it has been used for infection-resistant silver coating and for sealant coatings.

IBT is a powerful approach for surface micro-machining processing of medical devices. It can produce various kinds of patterns in the surface of cell culture scaffold materials; as is thought to be essential in tissue engineering materials.

Acknowledgement

This work is in part supported by the National Advanced Materials Committee of China, grant number: 863-715-0080012 and by the PhD Program of Education, Ministry of China.

References

[1] R.J. Rodriguez, The Sprint data base of ion implantation centers, 2nd ed., 1994, European Community Programme for Innovation and Technology Transfer.
[2] P. Sioshansi, E.J. Tobin, Surf. Coat. Technol. 83 (1996) 175.
[3] S.I. Stupp, P.V. Braun, Science 277 (1997) 1242.
[4] L. Yu, in: Research on Biological Effects Induced by Ion Implantation in China, Atomic Energy Press, Beijing, 1993, p. 1.
[5] J. Charnley, D.K. Halley, Clin. Orthop. 112 (1975) 170.
[6] S.B. Goodman, R.C. Chin, S.S. Chiou, D.J. Schurman, S.T. Woolson, M.P. Masada, Clin. Orthop. 244 (1989) 182.
[7] A.V. Lombardi, Jr, T.H. Mallory, B.K. Vaughn, P. Drouillard, J. Bone Joint Surg., A 71 (1989) 1337.
[8] J.Q. Zhang, X.Z. Zhang, Z.T. Guo, H.D. Li, Mater. Res. Soc. Symp. Proc. 55 (1986) 228.
[9] G. Dearnaley, Nucl. Instrum. Methods 189 (1981) 117.
[10] P. Sioshansi, Nucl. Instrum. Methods B 2425 (1987) 767.
[11] W.C. Oliver, R. Hutchings, J.B. Pethica, Metall. Trans., A 15 (1984) 2221.
[12] P. Sioshansi, R.W. Oliver, F.D. Matthews, J. Vac. Sci. Technol. 3 (1985) 2670.
[13] R. Crowninshield, J. Lower, L. Gilbertson, C. Jacobs, H. Price,

F. Jones, Trans. 36th Annu. Meet. Orthoped. Res. Soc. 15 (1990) 470.
[14] F.Z. Cui, H.D. Li, X.Z. Zhang, Nucl. Instrum. Methods 209210 (1983) 881.
[15] S.K. Taylor, P. Serekian, M. Manly, Trans. 39th Annu. Meet. Orthoped. Res. Soc. 18 (1993) 503.
[16] Y. Suzuki, M. Kusakabe, M. Iwaki, K. Kusakabe, H. Akiba, S. Sato, Mater. Res. Soc. Symp. Proc. 110 (1989) 669.
[17] B.D. Ratner, J. Biomater. Sci. Polym. Ed. 4 (1992) 3.
[18] A.Z. Okkema, S.L. Cooper, Biomaterials 12 (1991) 668.
[19] D.J. Li, F.Z. Cui, Q.L. Feng, J. Zhao, Chinese Phys. Lett. 14 (1997) 531.
[20] D.J. Li, J. Zhao, Appl. Surf. Sci. 78 (1994) 195.
[21] D.J. Li, J. Zhao, H.Q. Gu, M.Z. Lu, F.Q. Ding, Q.Q. Zhang, Nucl. Instrum. Methods B 82 (1993) 57.
[22] J.B. Yang, L.J. Wu, L. Li, J.D. Wu, Z.L. Yu, Z.H. Xu, Science in China C 40 (1997) 107.
[23] X.M. He, W.Z. Li, H.D. Li, Y. Fan, Nucl. Instrum. Methods B 82 (1993) 528.
[24] F.Z. Cui, Z.S. Luo, Q.L. Feng, J. Mater. Sci.: Mater. Med. 8 (1997) 403.
[25] T.N. Kim, Q.L. Feng, Z.S. Luo, F.Z. Cui, J.O. Kim, Surf. Coat. Technol. 99 (1998) 20–23.
[26] Q.H. Chen, Masters Thesis, Tsinghua University, 1997.
[27] T.N. Kim, Q.L. Feng, J. Wu, J.O. Kim, J. Korean Vac. Soc. 6 (1997) 27–33.
[28] R. Bambauer, P. Mestres, R. Schiel, P. Sioshansi, Dialysis and Transplantation 24 (1995) 228.
[29] L. Lu, M.W. Jones, R.L.C. Wu, Bio-med. Mater. Eng. 3 (1993) 223.
[30] M. Allen, F. Law, N. Rushton, Clin. Mater. 17 (1994) 1.
[31] C. Du, X.W. Su, F.Z. Cui, X.D. Zhu, Biomaterials 19 (1998) 651.
[32] E. Wintermantel, J. Mayer, J. Blum, K.-L. Eckert, P. Luscher, M. Mathey, Biomaterials 17 (1996) 83.